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Altered circulating memory T cells in vitiligo cases followed NB-UVB therapy

Fuquan Lin | Xiukun Sun | Jiehao Lei | Ai-e Xu

Department of Dermatology, Hangzhou Third People's Hospital, Affiliated Hangzhou Dermatology Hospital, Zhejiang University School of Medicine, Hangzhou, China

Correspondence
Ai-E Xu, Department of Dermatology, Hangzhou Third People's Hospital, Affiliated Hangzhou Dermatology Hospital, Zhejiang University School of Medicine, Hangzhou, China.
Email: xuaiehz@msn.com

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Abstract

Background: Vitiligo represents a commonly diagnosed autoimmune disease caused by the depletion of epidermal melanocytes. Many subsets of T cells contribute to vitiligo pathogenesis, including resident and circulating memory T cells.

Objectives: To analyze the amounts of $CD4^+$ and $CD8^+$memory T-cell subsets in peripheral blood specimens from vitiligo patients and alterations caused by narrowband ultraviolet B (NB-UVB) phototherapy.

Methods: Circulating $CD4^+$ and $CD8^+$ central memory T (T_{CM}) and effector memory T (T_{EM}) cell frequencies in 33 patients with non-segmental vitiligo and 16 healthy donors were evaluated by flow cytometry. Related chemokine levels were also detected.

Results: Peripheral blood $CD4^+$ T_{CM} and $CD8^+$ T_{CM} counts were markedly reduced in vitiligo cases while they were higher in active vitiligo compared with stable vitiligo cases. Circulating $CD8^+$ T_{CM} frequency in vitiligo was closely related to disease duration. Interestingly, $CD4^+$ T_{CM} and $CD8^+$ T_{CM} frequencies, alongside CXCL9 and CXCL10 amounts in peripheral blood of patients with vitiligo, were significantly decreased after NB-UVB phototherapy.

Conclusions: Decreased frequencies of circulating $CD4^+T_{CM}$ and $CD8^+T_{CM}$ by NB-UVB suggest a possible immunosuppressive effect of phototherapy. The chemokines CXCL9 and CXCL10 are the bridge between circulating and skin resident memory T cells. NB-UVB blocks the homing of circulating memory T cells into vitiligo lesions by down-regulating CXCL9 and CXCL10. Targeting the above proteins could provide novel, durable treatment options to cure and prevent flares of this disease.

KEYWORDS
memory T-cell, NB-UVB, vitiligo

1 | INTRODUCTION

Vitiligo represents a chronic skin depigmenting pathology featuring melanocyte depletion in the epidermis, affecting 0.5% to 2% of the general population. Vitiligo involves polymorphisms in genes responsible for immune responses and melanogenesis. Altered inflammatory and immune responses are considered the essential mechanisms inducing the dysfunction and death of melanocytes.[1]

Direct injury of melanocytes is mostly induced by CD8+ T cells.[2] Other subsets of T cells, especially memory T cells, are also involved in the development, maintenance, and flares of vitiligo. Vitiligo is currently considered a memory skin disease.[3] Following

Fuquan Lin,·Xiukun Sun contributed equally to this work.

repigmentation, vitiligo lesions generally show recurrence at comparable anomic sites, indicating that resident memory T cells (T_{RM}) are likely involved. The vitiligo skin has high amounts of CD8 T_{RM} cells expressing CXCR3.[4] In addition to the skin, memory T cells such as effector (T_{EM}) and central (T_{CM}) memory T cells are also present in peripheral blood specimens from vitiligo cases. Meanwhile, circulating $CD4^+$ and $CD8^+$ T_{EM} show lower amounts in vitiligo.[5]

The functional relationship between skin T_{RM} and recirculating memory T cells in a vitiligo mouse model was characterized.[6] Both cell types sensed skin autoantigens long after disease stabilization, synthesizing IFN-γ, CXCL9, and CXCL10. Blocking T_{CM} recruitment to the skin using FTY720 or depleting circulating memory T cells using anti-Thy1.1 antibodies at low dose reverses the disease, suggesting T_{RM} cooperation with circulating memory T cells for disease maintenance. The chemokine ligands CXCL9 and CXCL10 both interact with CXCR3, inducing immune cell migration into tissues in multiple type 1 inflammatory diseases. CXCL9 and CXCL10 are critical in vitiligo, with overt functions in directed migration and guiding of $CD8^+$ memory T cells to the epidermis.[7]

Targeting memory T cells and the chemokine ligands CXCL9 andCXCL10might provide new, long-lasting options for vitiligo treatment. However, related clinical data are scarce, and whether the current treatment options for vitiligo impact these targets remains largely undefined. Therefore, the current work aimed to assess the influence of NB-UVB phototherapy, a method widely used to cure vitiligo, on the amounts of circulating memory T cells as well as peripheral blood CXCL9 and CXCL10 levels. The findings provide novel insights into potential therapeutic targets in vitiligo.

2 | PATIENTS AND METHODS

2.1 | Patients

Thirty-three non-segmental vitiligo(NSV) cases and 16 age- and sex-matched healthy individuals were recruited. Vitiligo cases were grouped based on the 6-point vitiligo disease activity (VIDA) scoring system.[8] This scale evaluates the recurrence or enlargement of lesions in a time period between<6 weeks and 1 year. Wood's lamp analysis of confetti-like or trichome lesions was also considered.[9,10] Patients with a VIDA score >1 and/or leukodermal lesions showing poorly delineated borders or confetti-like lesions were regarded as active vitiligo cases. Those with a VIDA score of 0 and −1 were considered to have stable disease for at least 1 year. All 33 cases of vitiligo were scored and grouped by VIDA, divided into active and stable vitiligo. Patients with pregnancy (females) or complications of thyroid, heart, liver, kidney, and/or infectious diseases, dermatomyositis, scleroderma, lupus erythematosus, tumors, and other immune-related diseases were excluded. This study had approval from the Ethics Committee of Hangzhou Third Hospital. Signed informed consent was provided by each patient.

2.2 | Flow cytometry

Peripheral blood mononuclear cell (PBMC) isolation was performed by density gradient centrifugation with Ficoll-Hypaque reagents (GE). T-cell subsets with various fluorochrome-labeled monoclonal antibodies were detected flow-cytometrically on a BD Fluorescence-activated cell sorting (FACS) Canto II (BD Biosciences), as directed by the manufacturer. FACSDiva (BD Bioscience) was employed for data analysis.

First, lymphocytes were gated, of which CD3+T cells were identified. Then, the percentages of $CD3^+CD4^+CD45RO^+CD62L^+CD197^+$ ($CD4^+$ T_{CM}), $CD3^+CD4^+CD45RO^+CD62L^-CD197^-$($CD4^+$ T_{EM}), $CD3^+CD8^+$ $CD45RO^+CD62L^+CD197^+$($CD8^+$ T_{CM}), and $CD3^+CD8^+CD45RO^+$ $CD62L^-CD197^-$($CD8^+$ T_{EM}) T lymphocytes were determined.

2.3 | Serum chemokine assay

Blood was centrifuged at 330 × g (10 minutes) for preparing serum specimens, which were assessed by enzyme-linked immunosorbent assays (ELISA). Serum CXCL9/CXCL10 levels were determined with the Human MIG/IP-10 ELISA Kit (Sigma) as directed by the manufacturer.

2.4 | NB-UVB phototherapy

Twenty-two vitiligo cases underwent NB-UVB phototherapy, employing a Waldmann UV therapy system, equipped with Phillips TL-01 fluorescent lamps (radiation spectrum, 310-315 nm; peak, 311 nm). According to the distribution and area of leukoplakia, an appropriate instrument was selected for phototherapy, including a full-body cabinet, a half-body cabinet, or local radiation. NB-UVB therapy was performed thrice weekly on non-consecutive days for 10 weeks. Radiation was started at 400 mJ/cm^2, with a gradual increase by 10%-20% in subsequent sessions according to patient response and tolerance, until the minimal erythema dose (MED) was reached. In case of symptomatic erythema (burning and/or pain) or blisters, treatment was discontinued until symptoms are resolved; subsequent therapy started with the final dose before symptomatic erythema detection. Circulating memory T cells and CXCL9 and CXCL10 levels were evaluated before and after the phototherapy.

2.5 | Statistical analyses

Statistical Package for the Social Sciences (SPSS) 19.0 (SPSS) was employed for data analysis. Unpaired t test, the chi-square test, and the Wilcoxon signed rank test were performed for group comparisons. Spearman rank correlation analysis was carried out to assess the correlation between two quantitative parameters. $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient features

Thirty-three vitiligo cases were enrolled (19 females and 14 males). They were 35.15 ± 18.31 years old (range, 10-69 years). Sixteen healthy donors were also enrolled (10 females and 6 males), aged 27.00 ± 16.35 years(range, 20-62 years). Gender distribution and age were similar in the vitiligo group and normal controls. Of the 33 patients with vitiligo, 18 had active disease and 15 had stable disease. No significant difference was found in gender, age, disease course, or involved body area between the active and stable vitiligo groups($P > .05$) (Table 1).

3.2 | Frequencies of circulating memory T-cell subsets in vitiligo

The gating strategy in flow cytometry analysis of T_{CM} and T_{EM} is detailed in Figure 1. We compared the frequencies of $CD4^+$, $CD8^+$

TABLE 1 Comparison of active and stable vitiligo cases

	Stable vitiligo	Active vitiligo	*P*
Gender			
Male	7	7	.653
Female	8	11	
Age	34.27 ± 19.02	35.89 ± 18.21	.856
Disease duration (years)	8.83 ± 7.77	7.79 ± 5.18	.913
Affected body surface area (%)	5.07 ± 4.66	7.73 ± 12.21	.526

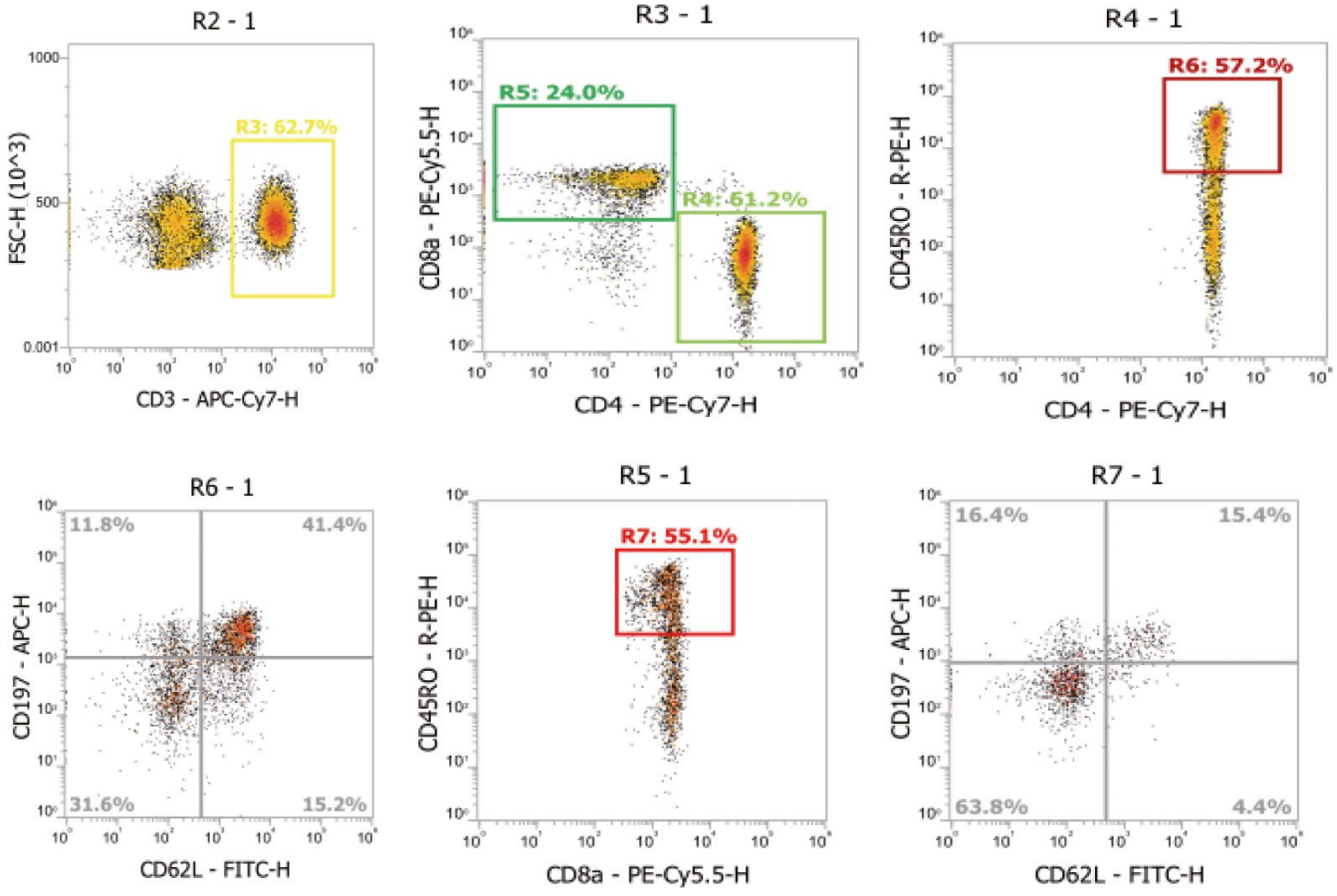

FIGURE 1 Flow cytometry analysis of memory T-cell subset levels in peripheral blood from a representative vitiligo case. The plots show the gating strategy: R4-1 indicates peripheral blood $CD3^+$ $CD4^+$ $CD45RO^+$ T lymphocytes; the upper right quadrant of R6-1 includes$CD3^+$ $CD4^+$ $CD45RO^+$ $CD62L^+$ $CD197^+$ T ($CD4^+$ T_{CM}) lymphocytes; the lower left quadrant of R6-1 includes$CD3^+$ $CD4^+$ $CD45RO^+$ $CD62L^-$ $CD197^-$ T ($CD4^+$ T_{EM}) lymphocytes. R5-1 shows peripheral blood $CD3^+$ $CD8^+$ $CD45RO^+$ T lymphocytes; the upper right quadrant of R7-1 includes$CD3^+$ $CD8^+$ $CD45RO^+$ $CD62L^+$ $CD197^+$ T ($CD8^+$ T_{CM}) lymphocytes; the lower left quadrant of R7-1 includes$CD3^+$ $CD8^+$ $CD45RO^+$ $CD62L^-$ $CD197^-$ T ($CD8^+$ T_{EM}) lymphocytes

T_{CM}, and T_{EM} subsets between vitiligo cases and healthy control individuals. Peripheral blood $CD4^+$ T_{CM} and $CD8^+$ T_{CM} counts were markedly decreased in vitiligo cases compared with healthy control individuals($P < .05$). In addition, $CD4^+$ T_{CM} and $CD8^+$ T_{CM} counts were remarkably increased in active vitiligo cases compared with individuals with stable vitiligo ($P < .05$). While $CD4^+$ T_{EM} and $CD8^+$ T_{EM} frequencies were comparable in the vitiligo and healthy control groups ($P > .05$), no significant difference in T_{EM} was found between the active and stable vitiligo subgroups ($P > .05$, Figure 2).

3.3 | Alterations of memory T-cell subsets and CXCL9 andCXCL10 levels in vitiligo by NB-UVB

The frequencies of $CD4^+$ and $CD8^+$ T_{CM} in peripheral blood samples from vitiligo cases after phototherapy were significantly lower than those before phototherapy($P < .05$). Those of $CD4^+$ T_{EM} and $CD8^+$ T_{EM} in vitiligo had no significant changes after phototherapy ($P > .05$). The levels of CXCL9 and CXCL10 in peripheral blood after phototherapy were significantly decreased compared with pre-phototherapy amounts ($P < .01$, Figure 3).

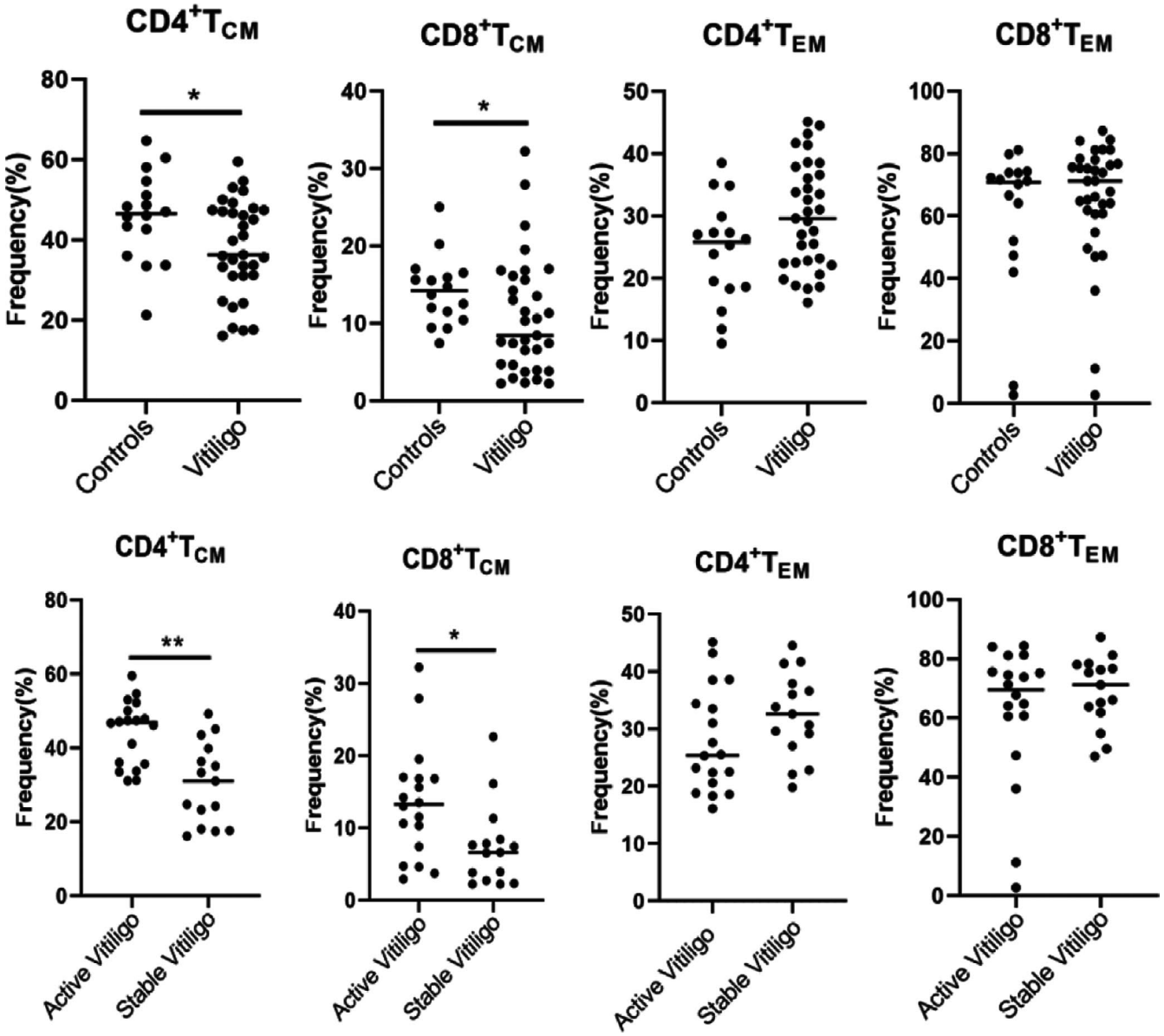

FIGURE 2 $CD4^+$ and $CD8^+$ T_{CM} and T_{EM} cells in peripheral blood specimens from vitiligo cases and healthy control individuals. Peripheral blood mononuclear cells were examined flow-cytometrically for circulating $CD4^+$ or $CD8^+$ T_{CM} and T_{EM} cell amounts. Peripheral blood $CD4^+$ T_{CM} and $CD8^+$ T_{CM} counts were markedly decreased in vitiligo cases compared with normal control individuals. No significant differences were found in$CD4^+$ $T_{EM}$and$CD8^+$ T_{EM} counts in vitiligo cases compared to healthy donors. $CD4^+$ T_{CM} and $CD8^+$ T_{CM} counts were higher in active vitiligo cases compared with the stable vitiligo group. *$P < .05$, **$P < .01$

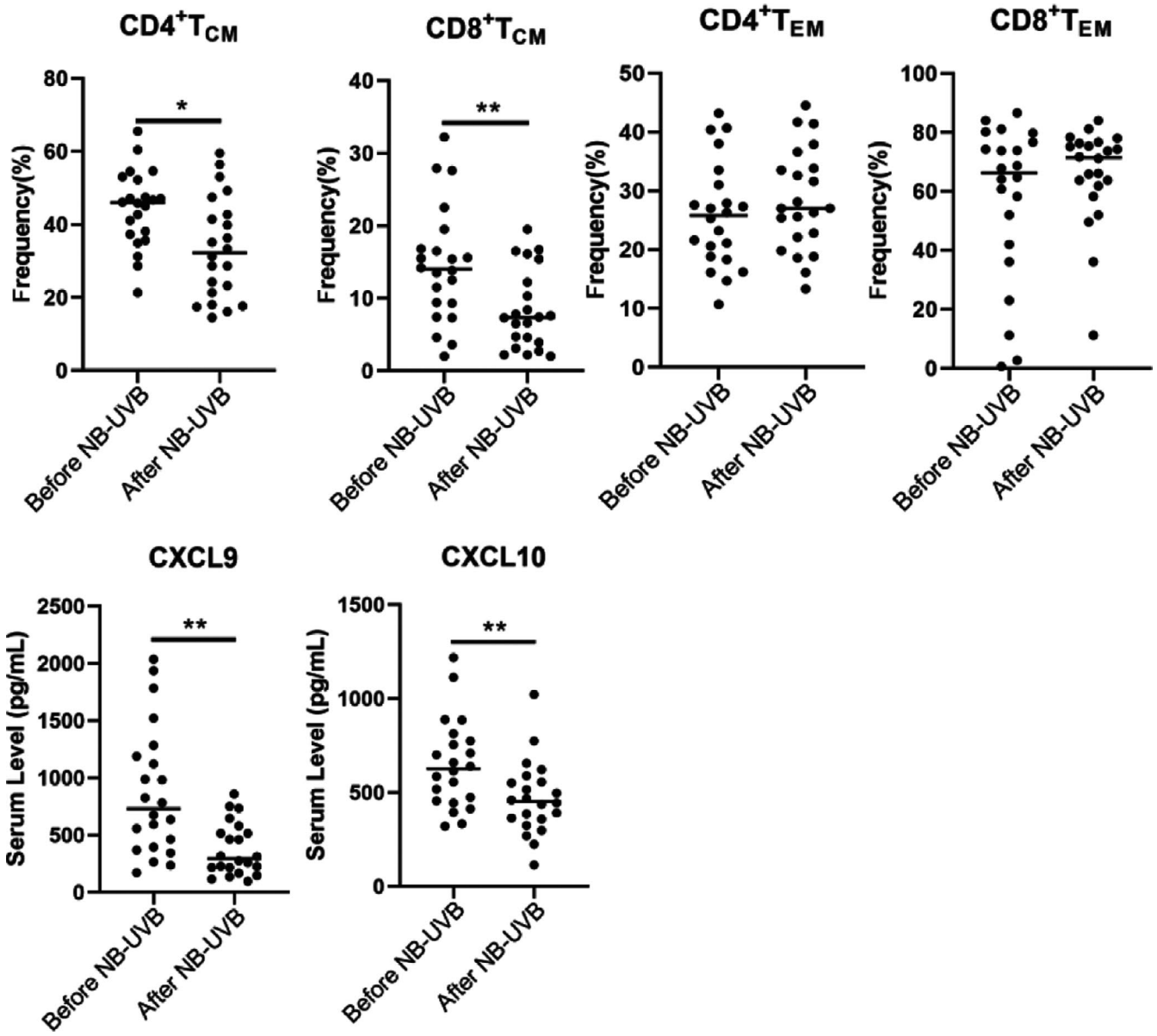

FIGURE 3 Alterations in memory T-cell subset frequencies and serum CXCL9 and CXCL10 levels by NB-UVB phototherapy. The frequencies of $CD4^+$ and $CD8^+$ T_{CM} in peripheral blood specimens from vitiligo cases after phototherapy were significantly lower than pre-phototherapy values ($P < .05$). $CD4^+$ T_{EM} and $CD8^+$ T_{EM} frequencies in vitiligo had no significant changes after phototherapy ($P > .05$). Serum CXCL9 and CXCL10 amounts, examined by enzyme-linked immunosorbent assay, were markedly decreased after NB-UVB treatment. $^*P < .05$, $^{**}P < .01$

3.4 | Correlation analysis

There were no significant associations of $CD4^+$ and $CD8^+$ memory T cells with affected body area in vitiligo patients ($P > .05$). The level of $CD8^+$ T_{CM} in peripheral blood was closely related to disease duration in vitiligo ($r = .391$, $P = .025$), while $CD4^+$ T_{CM}, $CD4^+$ T_{EM}, and $CD8^+$ T_{EM} amounts were not significantly related to disease duration ($P > .05$). Meanwhile, peripheral blood $CD4^+$ T_{CM}($r = .487$, $P = .004$) and $CD8^+$ T_{CM}($r = .489$, $P = .004$) counts were closely correlated with VIDA score, whereas T_{EM} showed no correlation ($P > .05$, Figure 4).

4 | DISCUSSION

Vitiligo constitutes a commonly diagnosed depigmentation skin pathology caused by melanocyte depletion, which can occur at any age, with no differences in gender and race. In 2011, segmental vitiligo was separated from other vitiligo types, referred to as non-segmental vitiligo, comprising acrofacial, mucosal, generalized, universal, mixed, and rare forms.[11] The pathogenesis of vitiligo is complex and has not been fully elucidated, mainly involving autoimmune, oxidative stress-related, genetic, and mental factors. The autoimmune hypothesis is the most recognized pathogenetic

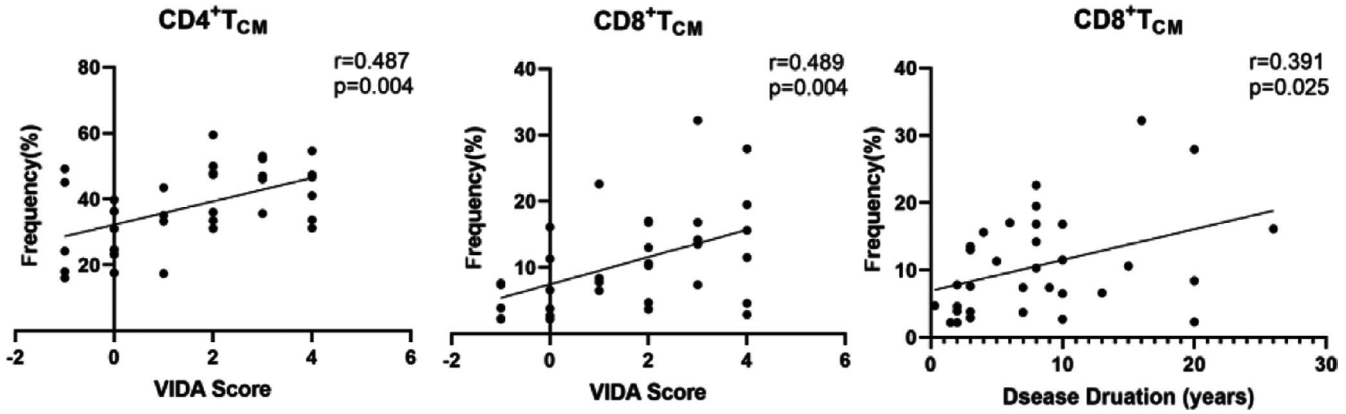

FIGURE 4 Associations of circulating memory T-cell subset frequencies with clinical manifestations in vitiligo. Spearman's correlation analysis confirmed positive associations of circulating $CD8^+$ T_{CM} frequency with disease duration, and of $CD4^+$ T_{CM} and $CD8^+$ T_{CM} amounts with VIDA score in patients with vitiligo

mechanism of NSV. $CD4^+$ T-cell amounts in peripheral blood specimens from NSV cases are abnormal, with Th1 and Th17 $CD4^+$ T remarkably increased.[12] In addition, relevant studies on cytotoxic $CD8^+$ T cells specifically targeting melanocytes supported the autoimmune hypothesis as the pathogenetic mechanism of vitiligo. Due to the important involvement of T cells in immune response to vitiligo and the high disease heterogeneity, more and more studies are focusing on T-cell abnormalities in patients with vitiligo, especially the role of memory T cells in vitiligo recurrence.

Two memory T-cell subsets were first reported with homing ability and effector functions, including central and effector memory T cells. T_{CM} express CCR7 (a chemokine receptor) and CD62L, enabling homing to lymphoid tissues where they undergo differentiation into effector T cells following induction by secondary stimuli. T_{EM} represent memory cells not constitutively expressing CCR7 and CD62L, which migrate to inflamed peripheral tissues and immediately show effector function.[13]

We detected the amounts of $CD4^+$ and $CD8^+$ memory T-cell subsets in peripheral blood specimens from vitiligo cases by multiparametric flow cytometry analysis. The results showed that memory T cells had abnormal amounts in patients with vitiligo. Indeed, peripheral blood $CD4^+T_{CM}$ and $CD8^+$ T_{CM} frequencies were markedly reduced in vitiligo cases compared with healthy control individuals. These results were consistent with another study which detected the decrease of circulating T_{CM} cells producing CLA or CCR6, suggesting T_{CM} redistribution into lymphoid organs and peripheral tissues.[5] Moreover, $CD4^+$ T_{CM} and $CD8^+$ T_{CM} counts were remarkably elevated in individuals with active vitiligo compared with stable vitiligo cases. Interestingly, $CD4^+$ T_{CM} and $CD8^+$ T_{CM} counts were positively associated with VIDA score. NB-UVB can decrease the quantities of $CD4^+$ T_{CM} and $CD8^+$ T_{CM}. Taken together, these data indicated that $CD4^+/CD8^+$ memory T-cell frequency is related to the severity of vitiligo. A recent study demonstrated that T_{CM} are found in healthy, non-inflamed human skin, lung, colon, and cervix, indicating that T_{CM} are involved in the primary immunosurveillance of peripheral tissues. In addition, T_{CM} have strong effector functions, with 80% of all CD8+ T_{CM} producing TC1/TC2/TC17/TC22 cytokines. T_{CM} can trigger inflammatory reactions in human skin-grafted mice by themself.[14] The role of circulating and resident T_{CM} in vitiligo should be further clarified. Based on the present research work, T_{CM} could be used as a biological marker or therapeutic target in vitiligo. A study examining contact hypersensitivity showed T-cell responses can be regulated by UVB, affecting both activated T-cell amounts and memory T-cell development in peripheral organs.[15] The decreases of $CD4^+$ T_{CM} and $CD8^+T_{CM}$ are also a UVB-induced immunosuppressive response like the above situation, but the exact mechanism is unknown.

NB-UVB also decreased the levels of the chemokines CXCL9 and CXCL10. This is consistent with another study reporting decreased CXCL10 amounts by averagely 42% following NB-UVB therapy for 24 sessions.[16] CXCL10 is one of the most reliable serum biomarkers of vitiligo activity.[17] IFN-g is critical for CXCL10 secretion and contributes to $CD8^+$ T-cell recruitment to injured skin via CXCR3.[18,19] In vitiligo cases, most $CD8^+$ T cells produce CXCR3 in skin lesions,[4] which show high CXCL9 and CXCL10 amounts.[20] The above report established IFN-γ-CXCR3-CXCL9/10 signaling as a major pathway controlling the directed migration and guiding of $CD8^+$ memory T cells to the epidermis.[7,21] Decreased peripheral CXCL9 and CXCL10 amounts could be caused by the lesional reduction of chemokines after NB-UVB phototherapy, which could be considered one of the pathways by which NB-UVB effects memory T cells in vitiligo.

The above data showed no marked differences in $CD4^+$ and $CD8^+$ T_{EM} properties between vitiligo cases and healthy control individuals, as well as between stable and active vitiligo cases. NB-UVB induced no $CD4^+$ or $CD8^+$ T_{EM} alterations. A previous study showed that skin $CD4^+$ and $CD8^+$ T cells from vitiligo (stable or active) cases display a T_{EM} phenotype ($CD45RO^+$ $CCR7^-$). $CD8^+$ T_{EM} amounts in vitiligo perilesional skin are starkly elevated by 13.4% and 25.1% compared with values obtained for control unaffected skin, in stable and active vitiligo cases, resepctively.[4] This suggests T_{EM} plays a more important role in vitiligo lesions than in peripheral blood. However, more details should be provided in further investigation.

This study had some limitations. The number of cases enrolled in each group was limited, which may lead to statistical bias. We did not detect T_{RM} in vitiligo lesions at the same time. However, peripheral blood samples are more accessible than skin biopsy for collecting memory T cells as clinical test items for judging the curative effect.

In conclusion, analysis of memory T cells in vitiligo showed circulating $CD4^+$ T_{CM} and $CD8^+$ T_{CM} frequencies are associated with disease severity and activity. In addition, NB-UVB treatment reduced circulating $CD4^+$ T_{CM} and $CD8^+$ T_{CM} amounts, suggesting a possible immunosuppressive effect of phototherapy. The chemokines CXCL9 and CXCL10 are the bridge between circulating and skin resident memory T cells. NB-UVB blocks the homing of circulating memory T cells into vitiligo lesions by down-regulating CXCL9 and CXCL10. There is a consensus on skin-resident memory T cells as a novel target for vitiligo treatment.[22] At the same time, attention should be paid to circulating memory T cells in vitiligo pathogenesis. Targeting the above molecules could provide novel, durable treatment options for cure and flare prevention in vitiligo.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings will be available in [repository name] at [DOI/URL] following an embargo from the date of publication to allow for commercialization of research findings.

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